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CLINICAL RESEARCH STUDIES

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The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins

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Objective: Cyanoacrylate (CA) embolization of refluxing great saphenous veins (GSVs) has been previously described. The outcomes from a multicenter study are still lacking.
Methods: A prospective multicenter study was conducted in seven centers in four European countries to abolish GSV reflux by endovenous CA embolization. Neither tumescent anesthesia nor postinterventional compression stockings were used. Varicose tributaries remained untreated until at least 3 months after the index treatment. Clinical examination, quality of life assessment, and duplex ultrasound evaluation were performed at 2 days and after 1, 3, 6, and 12 months.
Results: In 70 patients, of whom 68 (97.1%) were available for 12-month follow-up, 70 GSVs were treated. Two-day follow-up showed one proximal and one distal partial recanalization. Three additional proximal recanalizations were observed at 3-month (n = 2) and 6-month (n = 1) follow-up. Cumulative 12-month survival free from recanalization was 92.9% (95% confidence interval, 87.0%-99.1%). Mean (standard deviation) Venous Clinical Severity Score improved from 4.3 ± 2.3 at baseline to 1.1 ± 1.3 at 12 months. Aberdeen Varicose Vein Questionnaire score showed an improvement from 16.3 at baseline to 6.7 at 12 months (*P* < .0001). Side effects were generally mild; a phlebitic reaction occurred in eight cases (11.4%) with a median duration of 6.5 days (range, 2-12 days). Pain without a phlebitic reaction was observed in five patients (8.6%) for a median duration of 1 day (range, 0 - 12 days). No serious adverse event occurred. Paresthesia was not observed.
Conclusions: Endovenous CA embolization of refluxing GSVs is safe and effective without the use of tumescent anesthesia or compression stockings. (J Vasc Surg: Venous and Lym Dis 2015;3:2-7.)

Endovenous thermal ablation (EVTA) by radiofrequency or laser is a safe and effective treatment of refluxing great saphenous veins (GSVs) and has replaced traditional high ligation and stripping in official recommendations of various leading Vascular Societies in the United States[1] and the United Kingdom.[2] Whereas EVTA certainly is a successful treatment modality with limited downtime,[3-5] it requires the use of perivenous tumescent anesthesia and can still cause a variety of side effects like postoperative pain, bruising, and sensory nerve damage.[6,7] As an alternative treatment without the use of tumescent local anesthesia, foam sclerotherapy has also been engaged for treatment of refluxing saphenous veins, but anatomic 1-year success rates have been reported disappointingly low on the order of 70%.[8]

Table I. Eligibility criteria

Inclusion criteria
    Age ≥18 years and ≤70 years
    Symptomatic primary GSV incompetence diagnosed by clinical symptoms, with or without visible varicosities, and confirmed by duplex
    ultrasound imaging
    GSV on standing preprocedure Doppler ultrasound examination ≥3 mm and ≤10 mm (maximum diameter)
    CEAP classification of C2, C3, or C4
    Ability to walk unassisted
    Ability to attend follow-up visits
    Ability to understand the requirements of the study and to provide written informed consent
Exclusion criteria
    Life expectancy <1 year
    Regular pain medication
    Anticoagulation including heparin or coumadin
    Previous deep venous thrombosis
    Previous superficial thrombophlebitis in GSV
    Previous venous treatment on target limb
    Known hypercoagulable disorder
    Conditions that prevent routine vein treatment, like acute disease, immobilization or inability to ambulate, and pregnancy
    Tortuous GSV that will limit catheter placement in the opinion of the investigator (≥2 primary access sites are not allowed)
    Incompetent ipsilateral small saphenous vein or anterior accessory GSV
    Known sensitivity to the CA adhesive
    Participation in another clinical study involving an investigational agent or treatment within 30 days of enrollment

CA, Cyanoacrylate; *CEAP,* Clinical, Etiologic, Anatomic, and Pathologic classification; *GSV,* great saphenous vein.

An embolizing treatment of refluxing GSVs using a specific cyanoacrylate (CA) adhesive has recently been described, and 2-year follow-up of first-in-man use has just been reported.[9] Endovenously delivered CA immediately occludes the vessel. It elicits a granulomatous foreign body reaction and a concomitant inflammatory vein wall reaction, leading to subsequent fibrotic degradation.[9] CA as a well-understood substance[10-14] already in use in other medical devices is potentially advantageous for abolition of saphenous vein reflux because (1) it does not require the use of tumescent anesthesia; (2) by chemically bonding vein walls to each other, it obviates the need for postinterventional compression stockings; and (3) it precludes the risk of treatment-related sensory nerve damage.

This paper describes the 1-year-results of the prospective European multicenter cohort study that was initiated in December 2011, shortly after approval by European regulatory authorities (CE mark) and subsequent commercialization of endovenous use of CA adhesive.

METHODS

Study design. This prospective, multicenter clinical study on endovenous CA embolization of refluxing GSVs (NCT01570101) was performed in seven specialized vein centers in four European countries. Each site obtained local ethics committee approval before initiation, and all participants signed an ethics committee-approved, study-specific informed consent form before participation. Consecutive patients were included if they had symptomatic GSV incompetence with or without visible varicosities confirmed by duplex ultrasound imaging and a Clinical, Etiologic, Anatomic, and Pathologic (CEAP) stage of C2, C3, or C4. Additional inclusion and exclusion criteria were used as listed in Table I. Before treatment, patients underwent clinical examination, including CEAP classification and

Venous Clinical Severity Score (VCSS) and duplex ultrasound examination of the vein system; in addition, patients completed the EQ-5D quality of life survey[15] and the Aberdeen Varicose Vein Questionnaire (AVVQ).[16] Patients returned to the clinic at 48 hours and at 1, 3, 6, and 12 months. At each clinic visit, patients underwent physical examination, CEAP classification, VCSS, and assessment of potential adverse events and duplex ultrasound examination of the target limb. All physical examinations and duplex ultrasound examinations were performed by the local investigator or by staff under his supervision. Patients also completed EQ-5D and AVVQ. Reintervention and adjunctive vein treatment for potentially remaining tributaries at the target limb were disallowed until after the 3-month visit was complete.

Procedure technique. Endovenous embolization of the GSV with the proprietary Sapheon VenaSeal (Sapheon Inc, Morrisville, NC) CA adhesive and delivery system was performed as described previously.[17] In brief, the delivery system consists of a 7F introducer sheath/dilator, a 5F delivery catheter, a 3-mL syringe, and a dispenser gun. The 5F delivery catheter has a hydrophobic coating to prevent adhesion to delivered CA as well as air-filled microchannels to enhance sonographic visibility. Each pull of the trigger delivers 0.09 mL of CA. Sapheon CA is a custom formulation of CA, having properties of rapid polymerization when it is exposed to an aqueous environment, high viscosity, and plasticizers to enhance flexibility in its final polymerized state. The GSV is accessed at the distal point of reflux percutaneously with a micropuncture introducer kit (Cook, Bloomington, Ind), followed by insertion of a 0.035-inch J guidewire (Cook). With use of ultrasound control, a 7F introducer sheath/dilator is advanced to the saphenofemoral junction (SFJ) and positioned approximately 5 cm caudal to the SFJ. The distance of 5 cm was

chosen both to give space for ultrasound compression between the delivery catheter and the SFJ and to allow slight glue propagation toward the SFJ after injections. The 3-mL syringe containing CA extracted from its shipping vial is attached to the delivery catheter. The catheter is primed with the dispenser gun to fill all but the final 3 cm of catheter tubing. The primed delivery catheter is inserted into the introducer sheath and secured with a spin-lock mechanism. Then 5 cm of the catheter tip is exposed distal to the sheath tip and positioned 5 cm from the SFJ. After leg elevation of about 15 degrees, CA delivery consists of an initial double CA injection spaced 1 cm apart, followed by a 3-cm pullback and 3-minute localized compression directly over the injected vein segment. Repeated injections of CA followed by pullbacks of 3 cm and 30-second localized compressions of delivered CA then take place until the entire targeted vein segment is treated. The catheter is removed and compression applied to the catheter entry site until hemostasis is achieved. A single small bandage is applied, and venous occlusion is confirmed by duplex ultrasound. Patients were discharged and instructed to resume normal activities, avoiding strenuous activities for 1 day.

Statistical evaluation. As CA embolization is a novel embolization technique in the field of venous disease, the study's primary end point was the proportion of patients with complete occlusion of the target vein at 6-month duplex ultrasound evaluation. Whereas closure of the target vein promotes improved clinical symptoms in almost all patients, some cases have improvement already with only partial closure. For this reason, direct assessment of vein closure was chosen to be more informative compared with clinical scores with respect to a more accurate measure of the device's efficacy.

Complete occlusion was defined as no segments of patency longer than 10 cm.[18] As a secondary analysis of the complete occlusion rate, the proportion of patients with freedom from >10 cm of recanalization was tabulated by life-table methods and plotted with Kaplan-Meier analysis. The study's secondary end point was the rate of all adverse events. Changes from baseline in VCSS, AVVQ, and the general quality of life tool EQ-5D were evaluated by repeated measures analysis of variance. P values $< .05$ were considered statistically significant. Calculations were performed with SAS (version 9.0; Cary, NC) or R.[19]

RESULTS

Between December 2011 and July 2012, 70 patients were enrolled. Participating centers in the order of authors included 20, 15, 11, 10, 7, 4, and 3 patients, respectively. Fifty-five patients (78.6%) were women; mean (range) age and body mass index were 48.4 years (22-72 years) and 25.6 (18.9-43.4), respectively. Mean GSV diameter at the SFJ was 7.8 ± 2.1 mm (range, 6.6-14.0 mm). General risk factors included a family history of venous disease (n = 21), cigarette smoking (n = 9), hypertension (n = 5), abnormal blood lipids (n = 4), obesity (n = 4), and diabetes mellitus (n = 3).

Anatomic results. All enrolled patients received a technically successful study procedure. Thirty-four patients (49%) underwent treatment of the left GSV. Forty patients (57%) had no ultrasound-detectable tributaries in the treatment zone; 23 (33%) had one or two tributaries, and seven (10%) had more than two tributaries. Four patients (6%) had perforating veins in the treatment zone. All tributaries or perforators were left untreated for at least 3 months after study treatment. Mean treated vein length was 37.6 cm (range, 7-72 cm). Average net treatment time measured from catheter in to catheter out was 18.6 minutes (range, 8-74 minutes). Immediately after the procedure, all but one patient had complete closure of the target GSV. This single case still showed flow in the proximal 20 cm of the GSV fed through a large tributary entering at the distal point of flow. To achieve full occlusion, foam sclerotherapy was injected immediately, resembling a protocol deviation. At 48 hours, this GSV was fully occluded and remained so during 12 months of follow-up.

Sixty-eight patients (97.1%) were available for the 12-month visit. During 12 months of follow-up, a total of five patients were detected with partial recanalization, defined as patency in the treated segment by duplex ultrasound examination of more than 10 cm. Two of these patients had recanalization observed at 48 hours of follow-up, two at 3 months, and one at 6 months. All but one case showed patency originating at the SFJ; this case, which had recanalization at the distal 20 cm of the CA-embolized GSV segment, was noticed at 2-day follow-up. The proximal part of the GSV in this case, however, remained occluded until 12-month follow-up. The other case with recanalization at 48 hours presented with a proximal open GSV segment of 25 cm in length but was observed closed at 1-month follow-up and recanalized again after 3 months. The distal segment of the GSV, however, remained occluded until 12-month follow-up.
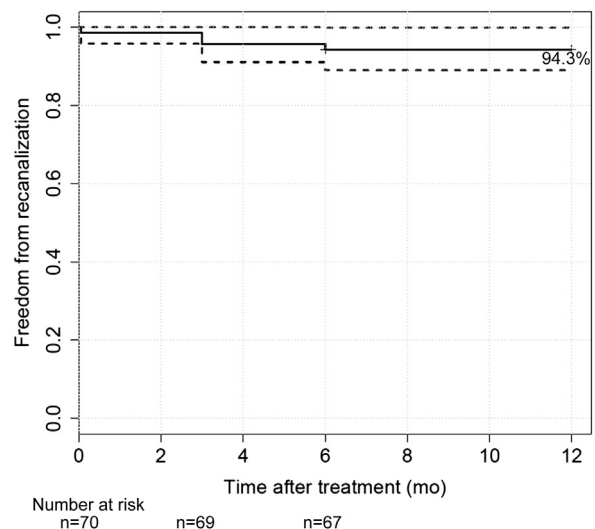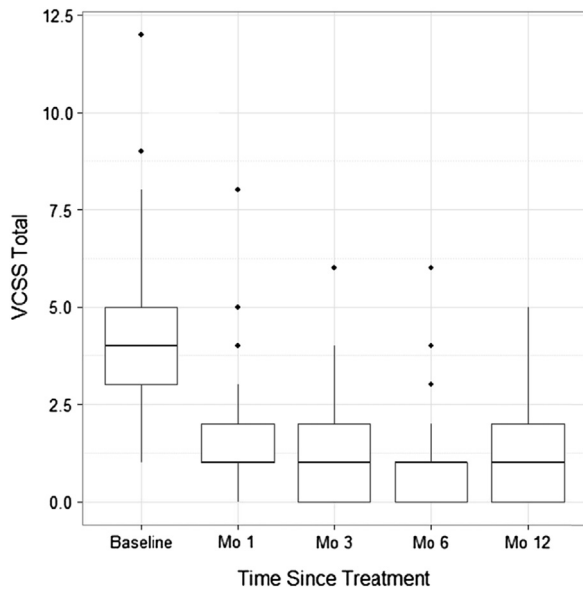

Fig 1. Survival free from recanalization of the target vein.

Fig 2. Change in Venous Clinical Severity Score (*VCSS*) by time since treatment.

At 3 months of follow-up, two additional cases were observed with a proximal GSV recanalization of 12 and 25 cm, respectively, both with a durable GSV occlusion distally. The last recanalization at 6-month follow-up presented as a microchannel recanalization of the proximal 20 cm of the GSV. Noteworthy, none of the patients with recanalization appeared to become clinically symptomatic, and all recanalizations had junctions with large tributaries. By life-table methods, the 12-month complete occlusion rate was 92.9% (95% confidence interval, 87.0-99.1%) (Fig 1).

Clinical improvement. Patients showed significant improvement of venous symptoms after GSV embolization. VCSS improved from a mean of 4.3 at baseline to 1.1 at 12 months (Fig 2); changes in VCSS from baseline were
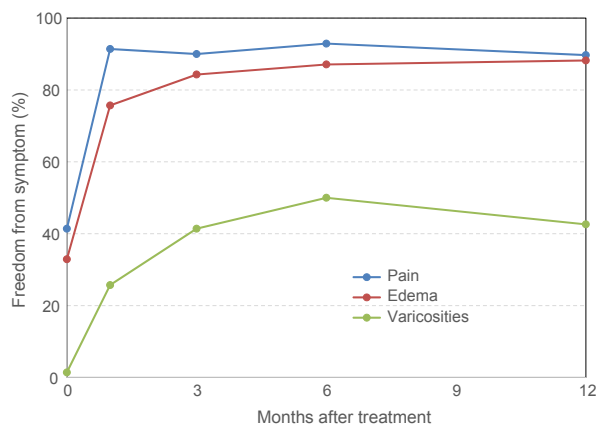
Fig 3. Proportion of patients free from varicosities, edema, and pain at baseline and during study follow-up.

statistically significant for all follow-up intervals ($P <$ .0001). There was no statistically significant difference between patients showing sustained occlusion of the once embolized GSV and those who experienced a partial recanalization during follow-up.

Remarkably, as indicated by VCSS subdomain scores, the proportion of patients whose target limbs were free from visible varicosities increased from 1.4% at baseline to 41.4% at 3 months of follow-up. Even more pronounced in the same period, the proportion of patients free from edema and pain increased from 41.4% and 32.9% at baseline to 90.0% and 82.1%, respectively. The improvements were largely preserved during 12-month follow-up (Fig 3).

Similarly, quality of life scores showed significant improvement (Table II). EQ-5D, which was modestly depressed at baseline, improved at all follow-up visits to near-maximum levels ($P =$ .0009). AVVQ score also improved significantly from a baseline value of 16.3 to 6.7 at 12 months ($P <$ .0001).

Side effects. Adverse events were mild and self-limited. Eight patients (11.4%) had a postprocedure phlebitic reaction along the treated vein or its tributaries defined as reddening of the overlying skin and pain on palpation. The median onset of symptoms was observed 6 days (range, 3-11 days) after the procedure; the median duration was 6.5 days (range, 2-12 days). Pain without phlebitic reaction was noticed in five patients (8.6%) for a median duration of 1 day (range, 0-12 days), starting at a median of 0 days (range, 0-3 days) after the procedure. Specific treatment of phlebitic reactions was under the discretion of the treating physician, but only two patients under this condition received nonsteroidal anti-inflammatory drugs for 2 and 15 days, respectively. No serious adverse event occurred, and moreover, paresthesia was not observed.

One patient (1.4%) developed a localized infection at the access point, and one (1.4%) had minor access point bruising. Finally, one patient (1.4%) had diagnosed prostate cancer 6 months after study treatment, which was deemed not related to the study treatment. One patient (1.4%) had glue extension measuring 6 mm beyond the SFJ recognized immediately after the procedure and still present at 1-year follow-up. Low-molecular-weight heparin was given for 2 weeks with spontaneous resolution. Thrombus extensions into the deep vein system were not observed.

DISCUSSION

EVTA is currently the "gold standard" for treatment of GSV reflux and is recommended as first-line therapy in the United States[1] and the United Kingdom.[2] Whereas EVTA produces high venous occlusion rates with limited downtime,[3-5] it requires at least perivenous tumescent anesthesia, which can cause postoperative pain, bruising, and other complications, such as sensory nerve damage,[6,7] even if the last risk is difficult to differentiate from heat damage during endothermal treatment. Ultrasound-guided foam sclerotherapy is also widely used because of its low cost and high versatility, but success rates for

Table II. Subject-rated scores by study visit

Visit	EQ-5D index	EQ-5D change from baseline	AVVQ	AVVQ change from baseline
Baseline	84.8 (15.7)	—	16.25 (7.99)	—
Month 1	96.9 (7.1)	12.0 (15.9)	9.76 (7.62)	−6.49 (8.16)
Month 3	96.8 (7.7)	12.0 (16.5)	7.62 (6.34)	−8.63 (7.50)
Month 6	96.6 (7.7)	11.7 (17.3)	6.28 (5.83)	−9.97 (8.36)
Month 12	94.5 (11.4)	9.5 (17.6)	6.67 (6.40)	−9.64 (8.99)

AVVQ, Aberdeen Varicose Vein Questionnaire.
All values shown are mean (standard deviation).

treatment of the GSV are as low as 75%,[8] with frequently needed repetitive treatment sessions. Sclerotherapy is also marred by postprocedure inflammation and staining, visual disturbances,[20,21] and, rarely, stroke related to paradoxical air embolism.[22-24] All of these treatments also require postoperative graduated compression stockings to support closure of the treated vein, compliance with which is well known to be frequently poor, particularly in countries with a predominantly sunny climate. Obviously, in our study, CA embolization treatment of refluxing GSVs does not necessarily require the use of graduated compression stockings. However, in this study, what benefit compression stockings could add under special circumstances like CA embolization of huge-diameter veins has not been formally evaluated. Unfortunately, we cannot say whether their use might have prevented some treatment failures.

Shortly after completion of the feasibility study on first-in-man use of CA for GSV embolization,[9,17] this European prospective multicenter cohort study was set up to obtain anatomic and clinical data from seven centers in four different countries, all with previous expertise in endothermal treatments of GSV reflux. The CA delivery system requires skill sets familiar to those who perform thermal vein ablation. The proprietary formulation used in the current clinical study was designed to have high viscosity, rapid polymerization, and a rubber-like elasticity once polymerized. The polymerized adhesive chemically bonds to the apposed intimal walls of the vein, effectively embolizing the vein by immediate closure. This, in general, is followed by a subacute inflammatory tissue response, a typical foreign body reaction, leading to a fibrotic transformation and degradation of glue and vein wall over time.

The closure rate reported herein was similar to that observed in a prior feasibility trial[9,17] and mirrors the efficacy of thermal techniques.[4,5] Per protocol, no adjunctive therapy like foam sclerotherapy or phlebectomy was performed until after the 3-month follow-up visit. Many comparable thermal clinical trials have allowed adjunctive therapy even at the time of study treatment[7] or shortly thereafter, theoretically increasing overall efficacy of study treatment. Remarkably, in the current study, we observed that all five cases of recanalization were somehow connected to untreated tributaries with high blood flow or even reflux. Identification and potential treatment of those large-diameter tributaries during the initial procedural visit would likely have increased the efficacy of CA embolization

of GSVs during routine treatments. Noteworthy, in this study, the anatomic results of CA embolization were achieved without the use of tumescent local anesthesia or graduated compression stockings. Even if not addressed in the current study, C5 and C6 patients should also be treatable by CA embolization as long as the principles of sterile administration of the glue are respected in venous ulcer patients. As expected, paralleling anatomic success of CA embolization, clinical outcomes measured by VCSS as well as patient-rated disease-specific (AVVQ) and generic quality of life measurements (EQ-5D) showed marked improvement. Improvements were both statistically significant and durable over the total follow-up time of 12 months. On the other hand, adverse events were generally mild and self-limited. Remarkably, unlike with thermal ablation or classic surgery, paresthesia was not recorded as a side effect of CA embolization in this study. A phlebitic reaction in the treatment zone and in untreated varicosities was the most common event in eight legs (11.4%); however, only two patients used nonsteroidal anti-inflammatory drugs to ameliorate it. Pain as an adverse event was noted in five more patients, of whom four required the use of analgesics. The rate of this kind of adverse event was in the range of thermal ablation of the GSV.[5] In the prior study of CA for varicose vein embolization,[8] 21% of treated legs showed thrombus extension, suggesting a risk of inadvertent glue embolization to the pulmonary arteries. Even if it is clinically without meaning and spontaneous resolution occurred without specific treatment, these observations of extensions to the deep vein system might have been a matter of concern to some physicians. In the current study, with adjusted instructions for use increasing the distance to the SFJ for placement of the first shot of CA, only one subject had a thrombus extension of 6 mm into the common femoral vein, suggesting that in conjunction with careful ultrasound monitoring during the first delivery of CA, glue embolization proximally can be reliably avoided. Treatment was 2 weeks with low-molecular-weight heparin; the thrombus extension resolved thereafter without any clinical sequelae.

CONCLUSIONS

In this prospective multicenter study on endovenous CA embolization of refluxing GSVs, CA proved safe and efficient, without the use of perivenous tumescent anesthesia and without postprocedure compression stockings.

However, further work is required to compare CA against endothermal ablation in randomized controlled trials.

AUTHOR CONTRIBUTIONS

Conception and design: TP, AD

Analysis and interpretation: TP, AD

Data collection: TP, JA, SD, LR, MW, JL, DC, AD

Writing the article: TP, AD, DC

Critical revision of the article: TP, JA, SD, LR, MW, JL, DC, AD

Final approval of the article: TP, JA, SD, LR, MW, JL, DC, AD

Statistical analysis: TP, AD, DC

Obtained funding: TP, JA, SD, LR, MW, JL, DC, AD

Overall responsibility: TP

REFERENCES

1. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53(Suppl):2S-48S.
2. Marsden G, Perry MC, Kelly K, Davies AH. Guideline Development Group. NICE guidelines on the management of varicose veins. BMJ 2013;347:f4279.
3. Proebstle TM, Krummenauer F, Gül D, Knop J. Nonocclusion and early reopening of the great saphenous vein after endovenous laser treatment is fluence dependent. Dermatol Surg 2004;30(Pt 1):174-8.
4. Van den Bos R, Arends L, Kockaert M, Neumann M, Nijsten T. Endovenous therapies of lower extremity varicosities: a meta-analysis. J Vasc Surg 2009;49:230-9.
5. Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg 2011;98:1079-87.
6. Almeida JI, Kaufman J, Göckeritz O, Chopra P, Evans MT, Hoheim DF, et al. Radiofrequency endovenous ClosureFAST versus laser ablation for the treatment of great saphenous reflux: a multicenter, single-blinded, randomized study (RECOVERY study). J Vasc Interv Radiol 2009;20:752-9.
7. Proebstle TM, Vago B, Alm J, Göckeritz O, Lebard C, Pichot O. Treatment of the incompetent great saphenous vein by endovenous radiofrequency powered segmental thermal ablation: first clinical experience. J Vasc Surg 2008;47:151-6.
8. Devereux N, Recke AL, Westermann L, Recke A, Kahle B. Catheter-directed foam sclerotherapy of great saphenous veins in combination with pre-treatment reduction of the diameter employing the principals of perivenous tumescent local anesthesia. Eur J Vasc Endovasc Surg 2014;47:187-95.
9. Almeida JI, Javier JJ, Mackay EG, Bautista C, Cher DJ, Proebstle TM. Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. Phlebology 2014 Apr 30; [Epub ahead of print].
10. Levrier O, Mekkaoui C, Rolland PH, Murphy K, Cabrol P, Moulin G, et al. Efficacy and low vascular toxicity of embolization with radical versus anionic polymerization of n-butyl-2-cyanoacrylate (NBCA). An experimental study in the swine. J Neuroradiol 2003;30:95-102.
11. Vinters HV, Galil KA, Lundie MJ, Kaufmann JC. The histotoxicity of cyanoacrylates. A selective review. Neuroradiology 1985;27:279-91.
12. Spiegel SM, Viñuela F, Goldwasser JM, Fox AJ, Pelz DM. Adjusting the polymerization time of isobutyl-2 cyanoacrylate. AJNR Am J Neuroradiol 1986;7:109-12.
13. Min RJ, Almeida JI, McLean DJ, Madsen M, Raabe R. Novel vein closure procedure using a proprietary cyanoacrylate adhesive: 30-day swine model results. Phlebology 2012;27:398-403.
14. Almeida JI, Min RJ, Raabe R, McLean DJ, Madsen M. Cyanoacrylate adhesive for the closure of truncal veins: 60-day swine model results. Vasc Endovascular Surg 2011;45:631-5.
15. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
16. Garratt AM, Macdonald LM, Ruta DA, Russell IT, Buckingham JK, Krukowski ZH. Towards measurement of outcome for patients with varicose veins. Qual Health Care 1993;2:5-10.
17. Almeida JI, Javier JJ, Mackay E, Bautista C, Proebstle TM. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. J Vasc Surg Venous Lymphat Disord 2013;1:174-80.
18. Khilnani NM, Grassi CJ, Kundu S, D'Agostino HR, Khan AA, McGraw JK, et al. Multi-society consensus quality improvement guidelines for the treatment of lower-extremity superficial venous insufficiency with endovenous thermal ablation from the Society of Interventional Radiology, Cardiovascular Interventional Radiological Society of Europe, American College of Phlebology and Canadian Interventional Radiology Association. J Vasc Interv Radiol 2010;21:14-31.
19. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing: Vienna, Austria; 2013. Available at: http://www.R-project.org/.
20. Guex JJ, Allaert FA, Gillet JL, Chleir F. Immediate and midterm complications of sclerotherapy: report of a prospective multicenter registry of 12,173 sclerotherapy sessions. Dermatol Surg 2005;31:123-8; discussion: 128.
21. Gillet JL, Guedes JM, Guex JJ, Hamel-Desnos C, Schadeck M, Lauseker M, et al. Side-effects and complications of foam sclerotherapy of the great and small saphenous veins: a controlled multicentre prospective study including 1,025 patients. Phlebology 2009;24:131-8.
22. Forlee MV, Grouden M, Moore DJ, Shanik G. Stroke after varicose vein foam injection sclerotherapy. J Vasc Surg 2006;43:162-4.
23. Bush RG, Derrick M, Manjoney D. Major neurological events following foam sclerotherapy. Phlebology 2008;23:189-92.
24. Ma RW, Pilotelle A, Paraskevas P, Parsi K. Three cases of stroke following peripheral venous interventions. Phlebology 2011;26:280-4.